EAST Search History

Ref #	Hits	Search Query	DBs	Default Operator	Plurals	Time Stamp
L1	43	presenilin associated	US-PGPUB; USPAT; DERWENT	ADJ	ON	2007/03/05 15:59
L2	1607	presenilin	US-PGPUB; USPAT; DERWENT	ADJ	ON	2007/03/05 15:47
L3	115	nicastrin	US-PGPUB; USPAT; DERWENT	ADJ	ON	2007/03/05 15:49
L4	9	nicastrin.ab.	US-PGPUB; USPAT; DERWENT	ADJ	ON	2007/03/05 15:48

10/763502
File 5:Biosis Previews(R) 1926-2007/Feb W4
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10 = 4-1-1999

Set	Items	Description
S1	22	PRESENILIN()ASSOCIATED
S2	421	PAMP
S3	2	S2 AND PRESENILIN
S4	294	NICASTRIN
S5	253	S4 AND PRESENILIN
S6	98	S5 AND HUMAN
S7	7	SEQUENCE AND S6
S8	6	APH()4
S9	123	S4 AND HUMAN

? t s1/7/1-22

1/7/1
DIALOG(R)File 5:Biosis Previews(R)

19420274 BIOSIS NO.: 200700080015
Phosphorylation and cleavage of %%%presenilin%%%-%%%associated%%% rhomboid-like protein (PARL) promotes changes in mitochondrial morphology
AUTHOR: Jeyaraju Danny V; Xu Liqun; Letellier Marie-Claude; Bandaru Sirisha ; Zunino Rodolfo; Berg Eric A; McBride Heidi M (Reprint); Pellegrini Luca
AUTHOR ADDRESS: Univ Laval, Ctr Rech Robert Giffard, 2601 Ch Canardiere, Quebec City, PQ G1J 2G3, Canada**Canada
AUTHOR E-MAIL ADDRESS: hmcbride@ottawaheart.ca; luca.pellegrini@crulrg.ulaval.ca
JOURNAL: Proceedings of the National Academy of Sciences of the United States of America 103 (49): p18562-18567 DEC 5 2006 2006
ISSN: 0027-8424
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: Remodeling of mitochondria is a dynamic process coordinated by fusion and fission of the inner and outer membranes of the organelle, mediated by a set of conserved proteins. In metazoans, the molecular mechanism behind mitochondrial morphology has been recruited to govern novel functions, such as development, calcium signaling, and apoptosis, which suggests that novel mechanisms should exist to regulate the conserved membrane fusion/fission machinery. Here we show that phosphorylation and cleavage of the vertebrate-specific P beta domain of the mammalian %%%presenilin%%%-%%%associated%%% rhomboid-like (PARL) protease can influence mitochondrial morphology. Phosphorylation of three residues embedded in this domain, Ser-65, Thr-69, and Ser-70, impair a cleavage at position Ser(77)-Ala(78) that is required to initiate PARL-induced mitochondrial fragmentation. Our findings reveal that PARL phosphorylation and cleavage impact mitochondria dynamics, providing a blueprint to study the molecular evolution of mitochondrial morphology.

1/7/2
DIALOG(R)File 5:Biosis Previews(R)

19324650 BIOSIS NO.: 200600670045
Association between the Leu262Val polymorphism of %%%presenilin%%% %%%associated%%% rhomboid like protein (PSARL), diabetes and metabolic phenotype in an Irish case-control population
AUTHOR: Hatunic Mensud (Reprint); Stapleton Mary; Ryan Anthony; Hand Elaine ; DeLong Ciara; Crowley Vivion; Nolan John J
AUTHOR ADDRESS: Dublin, Ireland**Ireland
JOURNAL: Diabetes 55 (Suppl. 1): pA258 JUN 2006 2006
CONFERENCE/MEETING: 66th Annual Meeting of the American-Diabetes-Association Washington, DC, USA June 09 -13, 2006; 20060609
SPONSOR: Amer Diabet Assoc
ISSN: 0012-1797
DOCUMENT TYPE: Meeting; Meeting Poster
RECORD TYPE: Citation
LANGUAGE: English

1/7/3
DIALOG(R)File 5:Biosis Previews(R)

19227587 BIOSIS NO.: 200600572982
Mitochondrial rhomboid PARL regulates cytochrome c release during apoptosis via OPA1-dependent cristae remodeling
AUTHOR: Cipolat Sara; Rudka Tomasz; Hartmann Dieter; Costa Veronica; Serneels Lutgarde; Craessaerts Katleen; Metzger Kristine; Frezza Christian; Annaert Wim; D'Adamio Luciano; Derks Carmen; Dejaegere Tim; Pellegrini Luca; D'Hooge Rudi; Scorrano Luca (Reprint); De Strooper Bart
AUTHOR ADDRESS: Venetian Inst Mol Med, Dulbecco Telethon Inst, Padua, Italy **Italy
AUTHOR E-MAIL ADDRESS: luca.scorrano@unipd.it; bart.destrooper@med.kuleuven.be
JOURNAL: Cell 126 (1): p163-175 JUL 14 2006 2006
ISSN: 0092-8674
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: Rhomboids, evolutionarily conserved integral membrane proteases, participate in crucial signaling pathways. %%%Presenilin%%%-%%%associated%%% rhomboid-like (PARL) is an inner mitochondrial membrane rhomboid of unknown function, whose yeast ortholog is involved in mitochondrial fusion. Parl(-/-) mice display normal intrauterine development but from the fourth postnatal week undergo progressive multisystemic atrophy leading to cachectic death. Atrophy is sustained by increased apoptosis, both in and ex vivo. Parl(-/-) cells display normal mitochondrial morphology and function but are no longer protected against intrinsic apoptotic death stimuli by the dynamin-related mitochondrial protein OPA1. Parl(-/-) mitochondria display reduced levels of a soluble, intermembrane space (IMS) form of OPA1, and OPA1 specifically targeted to IMS complements Parl(-/-) cells, substantiating the importance of PARL in

OPA1 processing. Parl(-/-) mitochondria. undergo faster apoptotic cristae remodeling and cytochrome c release. These findings implicate regulated intramembrane proteolysis in controlling apoptosis.

1/7/4
DIALOG(R)File 5:Biosis Previews(R)

19227575 BIOSIS NO.: 200600572970
OPA1 and PARL keep a lid on apoptosis
AUTHOR: Gottlieb Eyal (Reprint)
AUTHOR ADDRESS: Beatson Inst Canc Res, Canc Res UK, Apoptosis and Tumour Physiol Lab, Garscube Estate, Glasgow G61 1BD, Lanark, UK**UK
AUTHOR E-MAIL ADDRESS: e.gottlieb@beatson.gla.ac.uk
JOURNAL: Cell 126 (1): p27-29 JUL 14 2006 2006
ISSN: 0092-8674
DOCUMENT TYPE: Article; Editorial
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: A change in the shape of mitochondrial cristae must take place to attain rapid and complete release of cytochrome c during apoptosis. In this issue of Cell, Cipolat et al. (2006) and Frezza et al. (2006) show that a rhomboid intramembrane protease PARL and a dynamin-related protein OPA1 are critical regulators of cristae remodeling.

1/7/5
DIALOG(R)File 5:Biosis Previews(R)

18923367 BIOSIS NO.: 200600268762
Proteins related to schizophrenia and uses thereof
AUTHOR: St. George-Hyslop Peter H; Fraser Paul E
JOURNAL: Official Gazette of the United States Patent and Trademark Office Patents AUG 16 2005 2005
ISSN: 0098-1133
DOCUMENT TYPE: Patent
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: %%%Presenilin%%% %%%Associated%%% Membrane Protein (PAMP), and nucleic acids encoding this protein, are provided. PAMP and PAMP nucleic acids provide diagnostic and therapeutic tools for evaluating and treating or preventing neurodevelopmental and neuropsychiatric disorders. In a specific embodiment, mutations in PAMP are diagnostic for schizophrenia. The invention further relates to screening, particularly using high-throughput screens and transgenic animal models, for compounds that modulate the activity of PAMP and presenilins. Such compounds, or gene therapy with PAMP, can be used in treating neurodevelopmental and neuropsychiatric disorders, particularly schizophrenia. In addition, the invention provides PAMP mutants, nucleic acids encoding for PAMP mutants, and transgenic animals expressing PAMP mutants, which in a preferred aspect result in biochemical, morphological, or neuropsychological changes similar to those associated with schizophrenia.

1/7/6
DIALOG(R)File 5:Biosis Previews(R)

18876162 BIOSIS NO.: 200600221557
Self-regulated cleavage of the mitochondrial intramembrane-cleaving protease PARL yields P beta, a nuclear-targeted peptide
AUTHOR: Sik Attila; Passer Brent J; Koonin Eugene V; Pellegrini Luca (Reprint)
AUTHOR ADDRESS: CRULRG, Mol Neurobiol Lab, 2601 Chemin Canardiere, Quebec City, PQ G1J 2G3, Canada**Canada
AUTHOR E-MAIL ADDRESS: Luca.Pellegrini@crulrg.ulaval.ca
JOURNAL: Journal of Biological Chemistry 279 (15): p15323-15329 APR 9 2004 2004
ISSN: 0021-9258
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: Regulated intramembrane proteolysis (RIP) is an emerging paradigm in signal transduction. RIP is mediated by intramembrane-cleaving proteases (I-CliPs), which liberate biologically active nuclear or secreted domains from their membrane-tethered precursor proteins. The yeast Pcp1p/Rbd1p protein is a Rhomboid-like I-CliP that regulates mitochondrial membrane remodeling and fusion through cleavage of Mgm1p, a regulator of these essential activities. Although this ancient function is conserved in PARL ((P) under bar resenilins-(a) under bar ssociated (R) double under bar homboid-(1) under bar ike protein), the mammalian ortholog of Pcp1p/Rbd1p, the two proteins show a strong divergence at their N termini. However, the N terminus of PARL is significantly conserved among vertebrates, particularly among mammals, suggesting that this domain evolved a distinct but still unknown function. Here, we show that the cytosolic N-terminal domain of PARL is cleaved at positions 52-53(alpha-site) and 77-78 (beta-site). Whereas alpha-cleavage is constitutive and removes the mitochondrial targeting sequence, beta-cleavage appears to be developmentally controlled and dependent on PARL I-CliP activity supplied in trans. The beta-cleavage of PARL liberates Pbeta, a nuclear targeted peptide whose sequence is conserved only in mammals. Thus, in addition to its evolutionarily conserved function in regulating mitochondrial dynamics, PARL might mediate a mammalian-specific, developmentally regulated mitochondria-to-nuclei signaling through regulated proteolysis of its N terminus and release of the Pbeta peptide.

1/7/7
DIALOG(R)File 5:Biosis Previews(R)

18672630 BIOSIS NO.: 200600018025
Genetic variation in PSARL is associated with plasma insulin concentration
AUTHOR: Walder Ken R (Reprint); Blangero John; Jowett Jeremy B; Bayles Lyndal; Curran Joanne E; Elliott Kate S; Kim Kee-Hong; Skelton Joseph; Comuzzie Anthony G; Zimmet Paul Z; Collier Greg R; Kissebah Ahmed H
JOURNAL: Diabetes 54 (Suppl. 1): pA281 2005 2005
CONFERENCE/MEETING: 65th Annual Meeting of the

American-Diabetes-Association San Diego, CA, USA June 10 -14, 2005; 20050610
SPONSOR: Amer Diabet Assoc
ISSN: 0012-1797
DOCUMENT TYPE: Meeting; Meeting Poster
RECORD TYPE: Citation
LANGUAGE: English

1/7/8
DIALOG(R)File 5:Biosis Previews(R)

18672589 BIOSIS NO.: 200600017984
Functional characterisation of PSARL: Novel implications for the regulation of mitochondrial structure and function
AUTHOR: Kerr-Bayles Lyndal (Reprint); Bishara Natalie; Bayles Richard; Sanigorski Andrew; Segal David; Walder Ken; Collier Greg
JOURNAL: Diabetes 54 (Suppl. 1): pA272 2005 2005
CONFERENCE/MEETING: 65th Annual Meeting of the American-Diabetes-Association San Diego, CA, USA June 10 -14, 2005; 20050610
SPONSOR: Amer Diabet Assoc
ISSN: 0012-1797
DOCUMENT TYPE: Meeting; Meeting Poster
RECORD TYPE: Citation
LANGUAGE: English

1/7/9
DIALOG(R)File 5:Biosis Previews(R)

18580359 BIOSIS NO.: 200510274859
%%%Presenilin%%% %%%associated%%%, rhomboid-like protein: a mitochondrial intramembrane protease associated with insulin resistance and Type 2 diabetes
AUTHOR: Kerr-Bayles L J (Reprint); Walder K; Civitarese A; Jowett J; Curran J; Elliott K; Trevaskis J; Bishara N; Wanyonyi S; Sanigorski A M; Zimmet P; Blangero J; Kissebah A; Collier G R
AUTHOR ADDRESS: Deakin Univ, Metab Res Unit, Geelong, Vic 3217, Australia** Australia
JOURNAL: Diabetologia 47 (Suppl. 1): pA139 AUG 2004 2004
CONFERENCE/MEETING: 40th Annual Meeting of the European-Association-for-the-Study-of-Diabetes Munich, GERMANY September 05 -09, 2004; 20040905
SPONSOR: European Assoc Study Diabetes
ISSN: 0012-186X
DOCUMENT TYPE: Meeting; Meeting Abstract
RECORD TYPE: Citation
LANGUAGE: English

1/7/10
DIALOG(R)File 5:Biosis Previews(R)

17828936 BIOSIS NO.: 200400196569
Probing presenilin - like protease with a photoactivatable gamma - secretase inhibitor.
AUTHOR: Kornilova A Y (Reprint); Nyborg A C; Ladd T; Jansen K; Podlisny M B (Reprint); Golde T E; Wolfe M S (Reprint)
AUTHOR ADDRESS: Ctr. for Neurologic Dis., Brigham and Women's Hosp. and Harvard Med. Sch., Boston, MA, USA**USA
JOURNAL: Society for Neuroscience Abstract Viewer and Itinerary Planner 2003 pAbstract No. 239.11 2003 2003
MEDIUM: e-file
CONFERENCE/MEETING: 33rd Annual Meeting of the Society of Neuroscience New Orleans, LA, USA November 08-12, 2003; 20031108
SPONSOR: Society of Neuroscience
DOCUMENT TYPE: Meeting; Meeting Abstract
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: The gamma-secretase multiprotein complex, implicated in the pathogenesis of Alzheimer's disease, is an unusual intramembranous aspartyl protease, with %%%presenilin%%% %%%associated%%% with the catalytic component. Recently identified presenilin homologues (PSHs) with signature aspartate-containing motifs include signal peptide peptidase (SPP), which apparently acts as a single protein. Uncovering the workings of this "simpler" protease should accelerate understanding of the gamma-secretase mechanism. We previously showed that the active sites of SPP and gamma-secretase share similarities: a transition-state analog inhibitor of SPP moderately inhibits gamma-secretase in vitro and prevents an active-site directed gamma-secretase affinity reagent from labeling presenilin. In this study, we sought to probe the SPP active site with this same gamma-secretase affinity reagent. A photoactivated and biotinylated derivative of a (hydroxyethyl)urea-based transition-state analog inhibitor of gamma-secretase was used to photolabel V5-tagged SPP in cell lysates. We observed a specific labeling of SPP at a gel mobility corresponding to its homodimer. In addition, the photolabel was completely incapable of binding to SPP when one of the conserved aspartates was mutated. A number of structurally distinct gamma-secretase inhibitors were also examined for their ability to displace this photoprobe from SPP. Our observations further demonstrate the similarities between the SPP and PS active sites, indicate that the conserved aspartates are essential for binding an aspartyl protease transition-state analog, and raise questions about the oligomerization state of the active SPP.

1/7/11
DIALOG(R)File 5:Biosis Previews(R)

17111485 BIOSIS NO.: 200300070204
The novel presenilin-1-associated protein is a proapoptotic mitochondrial protein.
AUTHOR: Xu Xuemin (Reprint); Shi Yong-chang; Gao Wei; Mao Guozhang; Zhao Guojun; Agrawal Sudesh; Chisolm Guy M; Sui Dexin; Cui Mei-Zhen
AUTHOR ADDRESS: Dept. of Pathology, College of Veterinary Medicine, University of Tennessee, 2407 River Dr., Knoxville, TN, 37996, USA**USA
JOURNAL: Journal of Biological Chemistry 277 (50): p48913-48922 December 13, 2002 2002

MEDIUM: print
ISSN: 0021-9258
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: Recent studies have suggested a possible role for presenilin proteins in apoptotic cell death observed in Alzheimer's disease. The mechanism by which presenilin proteins regulate apoptotic cell death is not well understood. Using the yeast two-hybrid system, we previously isolated a novel protein, %%%presenilin%%%-%%%associated%%% protein (PSAP) that specifically interacts with the C terminus of presenilin 1 (PS1), but not presenilin 2 (PS2). Here we report that PSAP is a mitochondrial resident protein sharing homology with mitochondrial carrier protein. PSAP was detected in a mitochondria-enriched fraction, and PSAP immunofluorescence was present in a punctate pattern that colocalized with a mitochondrial marker. More interestingly, overexpression of PSAP caused apoptotic death. PSAP-induced apoptosis was documented using multiple independent approaches, including membrane blebbing, chromosome condensation and fragmentation, DNA laddering, cleavage of the death substrate poly(ADP-ribose) polymerase, and flow cytometry. PSAP-induced cell death was accompanied by cytochrome c release from mitochondria and caspase-3 activation. Moreover, the general caspase inhibitor benzyloxycarbonyl-Val-Ala-Asp-fluoromethyl-ketone, which blocked cell death, did not block the release of cytochrome c from mitochondria caused by overexpression of PSAP, indicating that PSAP-induced cytochrome c release was independent of caspase activity. The mitochondrial localization and proapoptotic activity of PSAP suggest that it is an important regulator of apoptosis.

1/7/12
DIALOG(R)File 5:Biosis Previews(R)

16643248 BIOSIS NO.: 200200236759
Activity-dependent isolation of the presenilin-gamma-secretase complex reveals nicastrin and a gamma substrate
AUTHOR: Esler William P; Kimberly W Taylor; Ostaszewski Beth L; Ye Wenjuan; Diehl Thekla S; Selkoe Dennis J (Reprint); Wolfe Michael S (Reprint)
AUTHOR ADDRESS: Center for Neurologic Diseases, Brigham and Women's Hospital, Harvard Medical School, 77 Avenue Louis Pasteur, Boston, MA, 02115, USA**USA
JOURNAL: Proceedings of the National Academy of Sciences of the United States of America 99 (5): p2720-2725 March 5, 2002 2002
MEDIUM: print
ISSN: 0027-8424
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: Presenilin heterodimers apparently contain the active site of gamma-secretase, a polytopic aspartyl protease involved in the transmembrane processing of both the Notch receptor and the amyloid-beta precursor protein. Although critical to embryonic development and the pathogenesis of Alzheimer's disease, this protease is difficult to characterize, primarily because it is a multicomponent complex of

integral membrane proteins. Here the functional gamma-secretase complex was isolated by using an immobilized active site-directed inhibitor of the protease. Presenilin heterodimers and nicastrin bound specifically to this inhibitor under conditions tightly correlating with protease activity, whereas several other presenilin-interacting proteins (beta-catenin, calsenilin, and %%%presenilin%%%-%%%associated%%% protein) did not bind. Moreover, anti-nicastrin antibodies immunoprecipitated gamma-secretase activity from detergent-solubilized microsomes. Unexpectedly, C83, the major endogenous amyloid-beta precursor protein substrate of gamma-secretase, was also quantitatively associated with the complex. These results provide direct biochemical evidence that nicastrin is a member of the active gamma-secretase complex, indicate that beta-catenin, calsenilin, and %%%presenilin%%%-%%%associated%%% protein are not required for gamma activity, and suggest an unprecedented mechanism of substrate-protease interaction.

1/7/13
DIALOG(R)File 5:Biosis Previews(R)

16520619 BIOSIS NO.: 200200114130
Nicastrin is required for Presenilin-mediated transmembrane cleavage in Drosophila
AUTHOR: Chung Hui-Min; Struhl Gary (Reprint)
AUTHOR ADDRESS: Department of Genetics and Development, College of Physicians and Surgeons, Howard Hughes Medical Institute, Columbia University, New York, NY, 10032, USA**USA
JOURNAL: Nature Cell Biology 3 (12): p1129-1132 December, 2001 2001
MEDIUM: print
ISSN: 1465-7392
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: The transmembrane glycoprotein Nicastrin was identified in a complex with the multipass membrane protein Presenilin. Presenilin mediates transmembrane cleavage of single-pass transmembrane proteins with short extracellular domains, including the ligand-activated form of the receptor Notch and beta-amyloid precursor protein (beta-APP). Transmembrane cleavage of Notch is essential for signal transduction, and transmembrane cleavage of beta-APP generates pathogenic amyloid peptides implicated in Alzheimer's disease. Here, we investigate the requirement for Nicastrin in Presenilin-mediated transmembrane cleavage. We show that, in Drosophila, loss of Nicastrin activity blocks the accumulation of %%%Presenilin%%% %%%associated%%% with the apical plasma membrane, abolishes Presenilin-dependent cleavage of the transmembrane domains of Notch and beta-APP, and abrogates Notch signal transduction.

1/7/14
DIALOG(R)File 5:Biosis Previews(R)

16385094 BIOSIS NO.: 200100556933
Proteomic analysis to identify molecular substrates for %%%presenilin%%%-%%%associated%%% gamma-secretase

AUTHOR: Jung K M (Reprint); Kim T W (Reprint)
AUTHOR ADDRESS: Taub Institute, Columbia University, New York, NY, USA**USA
JOURNAL: Society for Neuroscience Abstracts 27 (2): p1720 2001 2001
MEDIUM: print
CONFERENCE/MEETING: 31st Annual Meeting of the Society for Neuroscience San Diego, California, USA November 10-15, 2001; 20011110
ISSN: 0190-5295
DOCUMENT TYPE: Meeting; Meeting Abstract
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: gamma-Secretase is an unusual aspartyl protease that cleaves substrates within the transmembrane (TM) region. Functional presenilins are essential for gamma-secretase-mediated proteolysis of select membrane proteins, including APP and Notch. Virtually all FAD-linked mutations cause aberrant gamma-secretase activity, resulting the enhanced production of a longer and more amyloidogenic amyloid beta-peptide (Abeta42). Two of the characteristics of gamma-secretase include the lack of requirement for the specific primary sequences and the requirement for the signal-dependent ectodomain shedding, which implies that the presenilin may be involved in a general "off" mechanism for intracellular signaling by cleaving (and perhaps inactivating) the derivatives of multiple type-I TM proteins. We searched for not yet identified molecular substrates for %%%presenilin%%%-%%%associated%%% gamma-secretase using the proteomics approach. We first performed subcellular fractionation to isolate various membrane fractions using either the NT2 or 293 cells that were pre-treated with gamma-secretase inhibitors or stable cell lines that express inactive presenilin variants (e.g. PS1-D385A and PS2-D366A). The isolated membrane fractions were subjected to either carbonate extraction or Triton X-114 partitioning to achieve the further enrichment of TM proteins. The prepared samples were then separated on 2D-electrophoresis. Analyses of the integral membrane fractions from normal cells and gamma-secretase-inactive cells allowed us to detect several proteins (p71, p62, p51 and p34) that are only accumulated in gamma-secretase-inactive cells but not in normal cells. Further studies are in progress to determine the identities of these candidate gamma-secretase substrates utilizing mass spectrometry.

1/7/15
DIALOG(R)File 5:Biosis Previews(R)

16368555 BIOSIS NO.: 200100540394
A biochemical assay for the presenilin-dependent proteolysis of Notch: Similarities with the Y-secretase proteolysis of APP
AUTHOR: Esler W P (Reprint); Kimberly W T (Reprint); Vandrovec J D (Reprint); Ostaszewski B L (Reprint); Diehl T S (Reprint); Samuels M A (Reprint); Selkoe D J (Reprint); Wolfe M S (Reprint)
AUTHOR ADDRESS: Neurology, Brigham and Women's Hospital and Harvard Medical School, Boston, MA, USA**USA
JOURNAL: Society for Neuroscience Abstracts 27 (1): p1220 2001 2001
MEDIUM: print
CONFERENCE/MEETING: 31st Annual Meeting of the Society for Neuroscience San Diego, California, USA November 10-15, 2001; 20011110
ISSN: 0190-5295
DOCUMENT TYPE: Meeting; Meeting Abstract

RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: The presenilin-dependent transmembrane cleavage of the TACE-generated C-terminal fragment of Notch (NEXT) is required for release of the Notch intracellular domain (NICD), a critical signaling event in cell-fate decisions. This proteolytic cleavage has remarkable similarities to the Y-secretase mediated cleavage of the C-terminal fragment of APP (C99) that yields Abeta and P6. To analyze these cleavage events, we developed a recombinant Notch protein substrate termed N100Flag, a truncated form of the NEXT fragment of Notch 1. We compared the Y-secretase-like cleavage of this protein to that of the recombinant APP-based substrate C100Flag (Li et al., PNAS 97, 6138) using a cell-free assay. Incubating N100Flag or C100Flag with detergent solubilized Y-secretase from microsomes led to the formation of NICDFlag or P6Flag, respectively. Several structurally diverse Y-secretase inhibitors blocked these cleavages, and the rank order of potency was compared. Further, proteolysis of the two substrates showed similar pH optima. As reported for C100Flag, immunoprecipitating the presenilin complex brought down the proteolytic activity responsible for NICDFlag production. These data provide compelling biochemical evidence that the protease(s) responsible for the Y-secretase-like cleavage of Notch and APP are %%%presenilin%%% %%%associated%%% and are very similar or identical. These assays will be useful to understand the apparent differences in the intramembraneous cleavage sites in Notch and APP and in the purification of the Y-secretase complex.

1/7/16
DIALOG(R)File 5:Biosis Previews(R)

16367488 BIOSIS NO.: 200100539327
Overexpression of the novel presenilin-1-associated protein (PSAP) induces apoptosis
AUTHOR: Xu X M (Reprint); Shi Y C (Reprint); Cui M Z (Reprint); Gao W (Reprint); Zhao G J (Reprint); Mao G Z (Reprint)
AUTHOR ADDRESS: Pathology, Univ Tennessee, Knoxville, TN, USA**USA
JOURNAL: Society for Neuroscience Abstracts 27 (1): p1442 2001 2001
MEDIUM: print
CONFERENCE/MEETING: 31st Annual Meeting of the Society for Neuroscience San Diego, California, USA November 10-15, 2001; 20011110
ISSN: 0190-5295
DOCUMENT TYPE: Meeting; Meeting Abstract
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: Accumulating evidence has suggested a role of presenilin proteins in apoptosis observed in Alzheimer's disease. However, the mechanism by which presenilin proteins regulate apoptotic cell death is not well understood. Using the yeast two-hybrid system, we previously isolated a novel protein, PSAP (%%%presenilin%%%-%%%associated%%% protein) that specifically interacts with the C-terminus of presenilin 1 (PS1) but not presenilin 2 (PS2). Here we report that over-expression of PSAP induces apoptotic cell death. PSAP-induced apoptosis was documented using multiple independent approaches, including chromosome condensation and fragmentation, DNA laddering, cleavage of the death substrate

poly(ADP-ribose) polymerase, and flow cytometry. Apoptosis was observed in several different cell lines transfected with a vector expressing the PSAP gene. Furthermore, several fragments of PSAP, including the PDZ-like domain to which PS1 binds, were transiently expressed and it was demonstrated that the N-terminus and the PDZ-like domain of PSAP are required for its apoptotic activity. The essential role of PS1 in PSAP-induced apoptosis was further suggested by the enhancement of PSAP-induced apoptosis after increasing PS1 expression in N2a cells. These findings establish for the first time a molecular link between PS1 and an apoptotic cascade.

1/7/17
DIALOG(R)File 5:Biosis Previews(R)

16331972 BIOSIS NO.: 200100503811
%%%Presenilin%%%-%%%associated%%% gamma-secretase activity is not mandatory for calcium-related presenilin function
AUTHOR: Kim T W (Reprint); Chung S; Wolfe M S; Troy C (Reprint); Lee H M; Cheng I C; Pack-Chung E (Reprint); Yoo A S; Tanzi R E
AUTHOR ADDRESS: Taub Institute, Columbia University, New York, NY, USA**USA
JOURNAL: Society for Neuroscience Abstracts 27 (1): p630 2001 2001
MEDIUM: print
CONFERENCE/MEETING: 31st Annual Meeting of the Society for Neuroscience San Diego, California, USA November 10-15, 2001; 20011110
ISSN: 0190-5295
DOCUMENT TYPE: Meeting; Meeting Abstract
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: Presenilins (PS1 and PS2) appeared to be critical for the intramembrane proteolysis (e.g. gamma-secretase cleavage) of select transmembrane (TM) proteins, including APP and Notch. FAD-associated mutations in the presenilins give rise to an increased production of Abeta42. In addition to their proteolytic activity, the presenilins modulate the pathway for capacitative calcium entry (CCE), the refilling mechanism for depleted internal calcium stores (Yoo et al., Neuron 27,561-572 (2000)). Conformation coupling mediated by physical interaction between plasma membrane channels and ER constituents is shown to underlie a mechanism for CCE. To determine if proteolytic activity of the presenilins is required for CCE activity, we tested the effects of synthetic gamma-secretase inhibitors (IC50=apprx200 nM) on CCE. Both calcium imaging and electrophysiological studies showed that pretreatment with the inhibitor had virtually no effects on CCE, suggesting that the inhibitor-sensitive intramembrane proteolysis is not required for the presenilin-mediated regulation of CCE. Our recent studies also showed that enhanced coupling via overexpression of a putative CCE channel (e.g. TRPC6) antagonizes the molecular phenotypes of FAD mutant presenilins (e.g. reduced CCE and increased Abeta42). We propose that the presenilins directly regulate the conformational coupling between plasma membrane and ER, which simultaneously serves as a regulatory mechanism for gamma-secretase and CCE.

1/7/18
DIALOG(R)File 5:Biosis Previews(R)

16326609 BIOSIS NO.: 200100498448
Nicastrin and presenilin high molecular weight complexes modulate notch/glp-1 signal transduction and APP processing
AUTHOR: Yu G (Reprint); Nishimura M (Reprint); Arawaka A (Reprint); Levitan D (Reprint); Zhang Z (Reprint); Yu C (Reprint); Fraser P (Reprint); St George-Hyslop P (Reprint)
AUTHOR ADDRESS: University of Toronto, Toronto, M5S 3H2, Canada**Canada
JOURNAL: Journal of Neurochemistry 78 (Supplement 1): p142 September, 2001 2001
MEDIUM: print
CONFERENCE/MEETING: Eighteenth Biennial Meeting of the International Society for Neurochemistry and the Thirty-Second Annual Meeting of the American Society for Neurochemistry Buenos Aires, Argentina August 26-31, 2001; 20010826
ISSN: 0022-3042
DOCUMENT TYPE: Meeting; Meeting Abstract; Meeting Poster
RECORD TYPE: Citation
LANGUAGE: English

1/7/19
DIALOG(R)File 5:Biosis Previews(R)

16008836 BIOSIS NO.: 200100180675
Rapid Notch1 nuclear translocation after ligand binding depends on %%%presenilin%%%-%%%associated%%% gamma-secretase activity
BOOK TITLE: Annals of the New York Academy of Sciences. The molecular basis of dementia
AUTHOR: Berezovska Oksana (Reprint); Jack Christine; McLean Pamela; Aster Jon C; Hicks Carol; Xia Weiming; Wolfe Michael S; Weinmaster Gerry; Selkoe Dennis J; Hyman Bradley T
BOOK AUTHOR/EDITOR: Growdon John H; Wurtman Richard J; Corkin Suzanne; Nitsch Roger M
AUTHOR ADDRESS: Alzheimer's Disease Research Laboratory, Massachusetts General Hospital, 149-13th Street, Charlestown, MA, 02129, USA**USA
SERIES TITLE: Annals of the New York Academy of Sciences 920 p223-226 2000
MEDIUM: print
BOOK PUBLISHER: New York Academy of Sciences {a}, 2 East 63rd Street, New York, NY, 10021, USA
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RECORD TYPE: Citation
LANGUAGE: English

1/7/20
DIALOG(R)File 5:Biosis Previews(R)

15925850 BIOSIS NO.: 200100097689
Presenilin-mediated modulation of calcium release-activated calcium current

(ICRAC)and the Abeta42 biogenesis
AUTHOR: Chung S (Reprint); Yoo A S; Cheng I; Saunders A J; Pack-Chung E; Tanzi R E; Kim T
AUTHOR ADDRESS: Massachusetts General Hospital, Harvard Medical School, Boston, MA, USA**USA
JOURNAL: Society for Neuroscience Abstracts 26 (1-2): pAbstract No.-474.9 2000 2000
MEDIUM: print
CONFERENCE/MEETING: 30th Annual Meeting of the Society of Neuroscience New Orleans, LA, USA November 04-09, 2000; 20001104
SPONSOR: Society for Neuroscience
ISSN: 0190-5295
DOCUMENT TYPE: Meeting; Meeting Abstract
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: Perturbed Ca2+ homeostasis is one of the characteristic molecular phenotypes associated with presenilin familial Alzheimer's disease (FAD) mutations. We have previously reported that the capacitative Ca2+ entry (CCE) response, which is triggered by an intracellular Ca2+ store depletion, is significantly attenuated in cells expressing FAD mutant presenilins as compared to wild-type presenilins. To begin to elucidate the underlying mechanism for reduced CCE in presenilin FAD mutant cells, we studied whether FAD-associated PS1 mutation directly affect the activity of Ca2+ release-activated Ca2+ channels (ICRAC), which is a Ca2+-specific putative plasma membrane channel. ICRAC channel activities were measured by whole-cell mode patch clamp technique using CHO or SY5Y cell lines stably expressing either wild-type or M146L FAD mutant forms of PS1. We found that ICRAC were severely impaired in the cells expressing mutant PS1 as compared to wild-type PS1, indicating that aberrant ICRAC may be responsible for attenuated CCE in cells harboring FAD mutant presenilins. We have also previously demonstrated that CCE pathway is directly coupled to the presenilin-dependent gamma-secretase activity. We next tested whether augmentation of CCE would directly modulate the biogenesis of Abeta42. For this purpose, we ectopically expressed constructs encoding three different isoforms of putative store-operated Ca2+ channels, termed TRP (e.g. TRP1, TRP3, and TRP6; gifts of Drs. Craig Montell and Lutz Birnbaumer). TRP3 and TRP6 overexpression potentiates CCE in cells expressing FAD mutant presenilins. Interestingly, the generation of Abeta42 was decreased by TRP-transfection as compared to untransfected M146L-PS1 cells. Thus, augmentation of CCE (through TRP or relevant cellular components) could potentially be employed to reduce %%%presenilin%%%-%%%associated%%% gamma-secretase activity, and therefore Abeta42 generation.

1/7/21
DIALOG(R)File 5:Biosis Previews(R)

15920521 BIOSIS NO.: 200100092360
Altered calcium signaling in cells lacking %%%presenilin%%%-%%%associated%%% gamma-secretase activity
AUTHOR: Leissring M A (Reprint); Haig B R; LaFerla F M
AUTHOR ADDRESS: University of California, Irvine, CA, USA**USA
JOURNAL: Society for Neuroscience Abstracts 26 (1-2): pAbstract No.-474.7 2000 2000

MEDIUM: print
CONFERENCE/MEETING: 30th Annual Meeting of the Society of Neuroscience New Orleans, LA, USA November 04-09, 2000; 20001104
SPONSOR: Society for Neuroscience
ISSN: 0190-5295
DOCUMENT TYPE: Meeting; Meeting Abstract
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: Mutations in the presenilin genes (PS1, PS2) are a leading cause of early-onset familial Alzheimer's disease (FAD). Two highly consistent consequences of presenilin mutations are: (1) increased gamma-secretase cleavage of the beta-amyloid precursor protein (APP) and (2) specific alterations of intracellular calcium signaling pathways, including enhanced calcium release from intracellular stores and deficits in capacitative calcium entry (Leissring et al., J. Cell Biol. 149, in press). To investigate the relationship between gamma-secretase activity and calcium dysregulation, we are studying calcium signaling in cell lines stably transfected with APP together with PS1 and PS2 constructs containing mutations in critical aspartyl residues required for gamma-secretase activity. Relative to untransfected cells, cells expressing APP alone exhibited a significant potentiation in calcium signals evoked by agonists coupled to the phosphoinositide signaling cascade. Calcium signals in cells co-expressing APP together with PS1 and PS2 aspartyl mutations were potentiated to a significantly greater extent and also showed alterations consistent with enhanced capacitative calcium entry. Comparable studies using fibroblasts from PS1 and PS2 knock-out mice are in progress. These results will establish the relationship between the gamma-secretase activity in the modulation of intracellular calcium signaling pathways.

1/7/22
DIALOG(R)File 5:Biosis Previews(R)

15309036 BIOSIS NO.: 200000027349
Presenilin-2 mutations modulate amplitude and kinetics of inositol 1,4,5-trisphosphate-mediated calcium signals
AUTHOR: Leissring Malcolm A; Parker Ian; LaFerla Frank M (Reprint)
AUTHOR ADDRESS: Dept. of Neurobiology and Behavior, University of California, Irvine, 1109 Gillespie Neuroscience Facility, Irvine, CA, 92697-4545, USA**USA
JOURNAL: Journal of Biological Chemistry 274 (46): p32535-32538 Nov. 12, 1999 1999
MEDIUM: print
ISSN: 0021-9258
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: Mutations in the two presenilin genes (PS1, PS2) account for the majority of early-onset familial Alzheimer's disease (FAD) cases. Converging evidence from a variety of experimental systems, including fibroblasts from FAD patients and transgenic animals, indicates that PS1 mutations modulate intracellular calcium signaling pathways. Despite the potential relevance of these changes to the pathogenesis of FAD, a

comparable effect for PS2 has not yet been demonstrated experimentally. We examined the effects of wild-type PS2, and both of the identified FAD mutations in PS2, on intracellular calcium signaling in Xenopus oocytes. Inositol 1,4,5-trisphosphate (IP3)-evoked calcium signals were significantly potentiated in cells expressing either of the PS2 mutations relative to wild-type PS2-expressing cells and controls. Decay rates of calcium signals were also significantly accelerated in mutant PS2-expressing cells in a manner dependent upon IP3 concentration. The finding that mutationsin both PS1 and PS2 modulate intracellular calcium signaling suggests that these disturbances may represent a common pathogenic mechanism of %%%presenilin%%%-%%%associated%%% FAD.

? t s3/7/1-2

3/7/1
DIALOG(R)File 5:Biosis Previews(R)

18923367 BIOSIS NO.: 200600268762
Proteins related to schizophrenia and uses thereof
AUTHOR: St. George-Hyslop Peter H; Fraser Paul E
JOURNAL: Official Gazette of the United States Patent and Trademark Office Patents AUG 16 2005 2005
ISSN: 0098-1133
DOCUMENT TYPE: Patent
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: %%%Presenilin%%% Associated Membrane Protein (%%%PAMP%%%), and nucleic acids encoding this protein, are provided. %%%PAMP%%% and %%%PAMP%%% nucleic acids provide diagnostic and therapeutic tools for evaluating and treating or preventing neurodevelopmental and neuropsychiatric disorders. In a specific embodiment, mutations in %%%PAMP%%% are diagnostic for schizophrenia. The invention further relates to screening, particularly using high-throughput screens and transgenic animal models, for compounds that modulate the activity of %%%PAMP%%% and presenilins. Such compounds, or gene therapy with %%%PAMP%%%, can be used in treating neurodevelopmental and neuropsychiatric disorders, particularly schizophrenia. In addition, the invention provides %%%PAMP%%% mutants, nucleic acids encoding for %%%PAMP%%% mutants, and transgenic animals expressing %%%PAMP%%% mutants, which in a preferred aspect result in biochemical, morphological, or neuropsychological changes similar to those associated with schizophrenia.

3/7/2
DIALOG(R)File 5:Biosis Previews(R)

16262555 BIOSIS NO.: 200100434394
%%%PAMP%%% and PARL, two novel putative metalloproteases interacting with the COOH-terminus of %%%presenilin%%%-1 and -2
AUTHOR: Pellegrini Luca; Passer Brent J; Canelles Matilde; Lefterov Ilyia; Ganjei J Kelly; Fowlkes B J; Koonin Eugene V; D'Adamio Luciano (Reprint)
AUTHOR ADDRESS: Dept. of Microbiology and Immunology, Albert Einstein

College of Medicine, 1300 Morris Park Avenue, Ullmann, Bronx, NY, 10461, USA**USA
JOURNAL: Journal of Alzheimer's Disease 3 (2): p181-190 April, 2001 2001
MEDIUM: print
ISSN: 1387-2877
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: The familial Alzheimer's disease gene products, %%%presenilin%%% -1 and %%%presenilin%%%-2 (PS1 and PS2), are involved in amyloid beta-protein precursor processing (AbetaPP), Notch receptor signaling, and programmed cell death. However, the molecular mechanisms by which presenilins regulate these processes remain unknown. Clues about the function of a protein can be obtained by seeing whether it interacts with another protein of known function. Using the yeast two-hybrid system, we identified two proteins that interact and colocalize with the presenilins. One of these newly detected %%%presenilin%%%-interacting proteins belongs to the FtsH family of ATP-dependent proteases, and the other one belongs to Rhomboid superfamily of membrane proteins that are highly conserved in eukaryotes, archaea and bacteria. Based on the pattern of amino acid residues conservation in the Rhomboid superfamily, we hypothesize that these proteins possess a metal-dependent enzymatic, possibly protease activity. The two putative proteases interacting with presenilins could mediate specific proteolysis of membrane proteins and contribute to the network of interactions in which presenilins are involved.

? t s7/7/1-7

7/7/1
DIALOG(R)File 5:Biosis Previews(R)

18774907 BIOSIS NO.: 200600120302
C-terminal PAL motif of %%%presenilin%%% and %%%presenilin%%% homologues required for normal active site conformation
AUTHOR: Wang Jun; Beher Dirk; Nyborg Andrew C; Shearman Mark S; Golde Todd E; Goate Alison (Reprint)
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AUTHOR E-MAIL ADDRESS: goate@icarus.wustl.edu
JOURNAL: Journal of Neurochemistry 96 (1): p218-227 JAN 2006 2006
ISSN: 0022-3042
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: The Alzheimer's disease-associated beta-amyloid peptide is produced through cleavage of amyloid precursor protein by beta-secretase and gamma-secretase. gamma-Secretase is a complex containing %%%presenilin%%% (PS) as the catalytic component and three essential cofactors: %%%Nicastrin%%%, anterior pharynx defective (APH-1) and %%%presenilin%%% enhancer-2 (PEN-2). PS and signal peptide peptidase (SPP) define a novel family of aspartyl proteases that cleave substrates within the transmembrane domain presumptively using two membrane-embedded

aspartic acid residues for catalysis. Apart from the two aspartate-containing active site motifs, the only other region that is conserved between PS and SPP is a PAL %%%sequence%%% at the C-terminus. Although it has been well documented that this motif is essential for gamma-secretase activity, the mechanism underlying such a critical role is not understood. Here we show that mutations in this motif affect the conformation of the active site of gamma-secretase resulting in a complete loss of PS binding to a gamma-secretase transition state analog inhibitor, Merck C. Analogous mutations in SPP significantly inhibit its enzymatic activity. Furthermore, these mutations also abolish SPP binding to Merck C, indicating that SPP and gamma-secretase share a similar active site conformation, which is dependent on the PAL motif. Exploring the amino acid requirements within this motif reveals a very small side chain requirement, which is conserved during evolution. Together, these observations strongly support the hypothesis that the PAL motif contributes to the active site conformation of gamma-secretase and of SPP.

7/7/2
DIALOG(R)File 5:Biosis Previews(R)

18694633 BIOSIS NO.: 200600040028
The chick embryo appears as a natural model for research in beta-amyloid precursor protein processing
AUTHOR: Carrodeguas J A; Rodolosse A; Garza M V; Sanz-Clemente A; Perez-Pe R; Lacosta A M; Dominguez L; Monleon I; Sanchez-Diaz R; Sorribas V; Sarasa M (Reprint)
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JOURNAL: Neuroscience 134 (4): p1285-1300 2005 2005
ISSN: 0306-4522
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: This study reveals that the chick embryo has active the machinery for the production and degradation of the amyloid beta peptide characteristic of Alzheimer's disease. We cloned the principal beta-amyloid precursor protein isoforms in the chick embryo and observed that they are highly homologous to the %%%human%%% sequences and identical at the C-terminal %%%sequence%%%, including the amyloid beta domain. Mammals such as rat or mouse, more commonly used as animal models of %%%human%%% diseases, have a distinct amyloid beta %%%sequence%%%. The distribution of beta-amyloid precursor protein isoforms in the chick embryo revealed that, as in humans, their expression is ubiquitous and the prototype beta-amyloid precursor protein-695 predominated in the nervous system. We also found that the chick embryo expresses the genes for the main proteolytic proteases implicated in the production of amyloid beta, including BACE-1, BACE-2, %%%presenilin%%%-1, %%%presenilin%%%-2 and %%%nicastrin%%%, as well as the amyloid beta-degrading enzyme neprilysin, or ADAM-17, a protease implicated in the non-amyloidogenic processing of beta-amyloid precursor protein. We have also found that between amyloid beta40 and amyloid beta42, this latter seems to be the major amyloid beta peptide produced during chick

embryogenesis. The chick embryo appears as a suitable natural model to study cell biology and developmental function of beta-amyloid precursor protein and a potential assay system for drugs that regulate beta-amyloid precursor protein processing.

7/7/3
DIALOG(R)File 5:Biosis Previews(R)

18433379 BIOSIS NO.: 200510127879
Rat %%%nicastrin%%% gene: cDNA isolation, mRNA variants and expression pattern analysis
AUTHOR: Confaloni Annamaria (Reprint); Crestini Alessio; Albani Diego; Piscopo Paola; Campeggi Lorenzo Malvezzi; Terreni Liana; Tartaglia Marco; Forloni Gianluigi
AUTHOR ADDRESS: Ist Super Sanita, Dept Cellular Biol and Neurosci, Viale Regina Elena 299, I-00161 Rome, Italy**Italy
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JOURNAL: Molecular Brain Research 136 (1-2): p12-22 MAY 20 05 2005
ISSN: 0169-328X
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: %%%Nicastrin%%% is a type I transmembrane glycoprotein that interacts with %%%presenilin%%%, Aph-1, and Pen-2 proteins to form a high molecular complex with gamma secretase activity. Then, %%%nicastrin%%% has a central role in %%%presenilin%%%-mediated processing of beta-amyloid precursor protein and in some aspects of Notch/glp-1 signaling in vivo. Here, we isolated a rat %%%nicastrin%%% cDNA and investigated gene expression in embryonic and adult rat tissues. The predicted amino acid %%%sequence%%% is comprised of 708 residues and showed a high degree of identity with other vertebrate orthologs. Besides full-length %%%nicastrin%%% mRNA, we identified an alternative spliced variant lacking the whole exon 3 and predicted to encode a 62-residue-long truncated protein. Full-length %%%nicastrin%%% mRNA was observed to be ubiquitously expressed, while the spliced variant was preferentially transcribed in the nervous system, whether in embryonic or adult neural tissues. Studies performed on primary cell cultures demonstrated that the short isoform was expressed in neurons, but not in astrocyte and microglial cells. Further experiments performed to verify the presence of the variant in neuroblastoma culture failed to show any truncated protein. Treatments by cyclohexamide showed the involvement of a quality control-based surveillance mechanism, which selectively degrades the exon 3-skipped isoform.In summary, this is the first report describing a novel skipped isoform of %%%nicastrin%%% which may suggest a new possible control mechanism based on the alternative splicing and nonsense-mediated mRNA decay to regulate brain protein expression and provide newer insights into potential implication in Alzheimer's disease. (c) 2005 Elsevier B.V.

7/7/4
DIALOG(R)File 5:Biosis Previews(R)

18242739 BIOSIS NO.: 200500149804
A %%%sequence%%% within the first transmembrane domain of PEN-2 is critical for PEN-2-mediated endoproteolysis of %%%presenilin%%% 1
AUTHOR: Kim Seong-Hun; Sisodia Sangram S (Reprint)
AUTHOR ADDRESS: Dept Neurobiol Pharmacol and Physiol, Univ Chicago, 947 E 58th St,MC0926, Chicago, IL, 60637, USA**USA
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JOURNAL: Journal of Biological Chemistry 280 (3): p1992-2001 January 21, 2005 2005
MEDIUM: print
ISSN: 0021-9258
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RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: Macromolecular complexes containing presenilins (PS), %%%nicastrin%%% (NCT), APH-1, and PEN-2 mediate the beta-secretase cleavage of the gamma-amyloid precursor protein and Notch. APH-1 and NCT stabilize the PS1 holoprotein, whereas PEN-2 is critical for endoproteolysis of PS1. To define the structural domains of PEN-2 that are necessary for mediating PS1 endoproteolysis and gamma-secretase activity, we coexpressed APH-1, NCT, and PS1 together with a series of PEN-2 mutants, which harbored deletions in hydrophilic segments, or chimeric PEN-2 molecules that contained heterologous transmembrane domains (TMDs). We now report that with the exception of the PEN-2 variants with deletions proximal to the TMDs, the vast majority of the deletion variants were functional. Mutants that were nonfunctional were also unstable but were rescued by transposition of a heterologous %%%sequence%%% containing conservative amino acid substitutions into the deleted region. Notably, the carboxyl-terminal hydrophilic domain of PEN-2 was dispensable for promoting PS1 endoproteolysis but was critical for stabilizing the resulting PS1 derivatives. More importantly, we demonstrated that a chimeric PEN-2 with a replacement of the TMD2 with the TMD1 from sterol regulatory element binding protein 1 (SREBP-1) is fully functional but that a chimeric PEN-2 with a replacement of the TMD1 with the TMD2 from SREBP-1 is not. The function of this latter chimera was rescued by the replacement of the proximal two-thirds of the SREBP-1 TMD2 with the proximal two-thirds of the authentic TMD1 from PEN-2. These results suggest that the proximal two-thirds of the PEN-2 TMD1 is functionally important for endoproteolysis of PS1 holoproteins and the generation of PS1 fragments, essential components of the gamma-secretase complex.

7/7/5
DIALOG(R)File 5:Biosis Previews(R)

17836787 BIOSIS NO.: 200400204420
Intramembrane proteolysis of %%%human%%% NotchdeltaE.
AUTHOR: Liu X F (Reprint); Gharahdaghi F; Sobotka-Briner C D; Tian G; Greenberg B
AUTHOR ADDRESS: Mol. Sci. Dept, AstraZeneca, Wilmington, DE, USA**USA
JOURNAL: Society for Neuroscience Abstract Viewer and Itinerary Planner 2003 pAbstract No. 729.11 2003 2003
MEDIUM: e-file

CONFERENCE/MEETING: 33rd Annual Meeting of the Society of Neuroscience New Orleans, LA, USA November 08-12, 2003; 20031108
SPONSOR: Society of Neuroscience
DOCUMENT TYPE: Meeting; Meeting Abstract
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: The major proteinaceous component of the amyloid deposit in Alzheimer's disease brain is Abeta, which is released from the beta-secretase-generated C99 fragment of APP by the subsequent proteolytic activity of gamma-secretase. Four protein components have been identified as essential for the catalytic activity of gamma-secretase, including %%%presenilin%%%, %%%nicastrin%%%, Aph-1 and Pen-2. In addition to APP, gamma-secretase has been demonstrated to cleave several other type I transmembrane proteins, such as Notch, ErbB4, e-cadherin and CD44. No common %%%sequence%%% specificities have been identified among these substrates. Within the APP C99 fragment, gamma-secretase is believed to hydrolyze at least 3 different sites, generating as a result Abeta40, Abeta42, and AICD (APP Intracellular Domain), while gamma-secretase-mediated cleavage at the S3 site in the Notch transmembrane domain produces NICD (Notch Intracellular Domain). In a recent report (Okochi, M et al. EMBO J 2002, 21(20), 5408), additional cleavage sites were identified in the Notch transmembrane domain using as a substrate Flag-tagged murine NotchDELTAE recombinantly expressed in HEK cells. We have identified similar cleavages within Flag-tagged %%%human%%% NotchDELTAE. However, immunoblot analysis indicated that the Flag-tag might interfere with the intramembranous proteolysis of Notch. Using %%%human%%% NotchDELTAE lacking the FLAG tag, we have demonstrated an effect of the tag on the cleavage specificity of gamma-secretase within the transmembrane domain of Notch. These results demonstrate the importance of assessing the impact of artificial recombinant domains on intramembranous substrate cleavage, and conclusions regarding cleavage specificities of this complex proteolytic activity when employing recombinant substrates.

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DIALOG(R)File 5:Biosis Previews(R)

17805479 BIOSIS NO.: 200400176236
A conserved GXXXG motif in APH-1 is critical for assembly and activity of the gamma-secretase complex.
AUTHOR: Lee Sheu-Fen; Shah Sanjiv; Yu Cong; Wigley W Christian; Li Harry; Lim Myungsil; Pedersen Kia; Han Weiping; Thomas Philip; Lundkvist Johan; Hao Yi-Heng; Yu Gang (Reprint)
AUTHOR ADDRESS: Center for Basic Neuroscience, University of Texas Southwestern Medical Center, 5323 Harry Hines Blvd., Dallas, TX, 75390-9111, USA**USA
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JOURNAL: Journal of Biological Chemistry 279 (6): p4144-4152 February 6, 2004 2004
MEDIUM: print
ISSN: 0021-9258
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: The multipass membrane protein APH-1, found in the gamma-secretase complex together with %%%presenilin%%%, %%%nicastrin%%%, and PEN-2, is essential for Notch signaling in Caenorhabditis elegans embryos and is required for intramembrane proteolysis of Notch and beta-amyloid precursor protein in mammalian and Drosophila cells. In C. elegans, a mutation of the conserved transmembrane Gly123 in APH-1 (mutant or28) leads to a notch/glp-1 loss-of-function phenotype. In this study, we show that the corresponding mutation in mammalian APH-1aL (G122D) disrupts the physical interaction of APH-1aL with hypoglycosylated immature %%%nicastrin%%% and the %%%presenilin%%% holoprotein as well as with mature %%%nicastrin%%%, %%%presenilin%%%, and PEN-2. The G122D mutation also reduced gamma-secretase activity in intramembrane proteolysis of membrane-tethered Notch. Moreover, we found that the conserved transmembrane Gly122, Gly126, and Gly130 in the fourth transmembrane region of mammalian APH-1aL are part of the membrane helix-helix interaction CXXXG motif and are essential for the stable association of APH-1aL with %%%presenilin%%%, %%%nicastrin%%%, and PEN-2. These findings suggest that APH-1 plays a GXXXG-dependent scaffolding role in both the initial assembly and subsequent maturation and maintenance of the active gamma-secretase complex.

7/7/7
DIALOG(R)File 5:Biosis Previews(R)

17096917 BIOSIS NO.: 200300055636
Mammalian APH-1 interacts with %%%presenilin%%% and %%%nicastrin%%% and is required for intramembrane proteolysis of amyloid-beta precursor protein and Notch.
AUTHOR: Lee Sheu-Fen; Shah Sanjiv; Li Hongqiao; Yu Cong; Han Weiping; Yu Gang (Reprint)
AUTHOR ADDRESS: Center for Basic Neuroscience, University of Texas Southwestern Medical Center, 5323 Harry Hines Blvd., Dallas, TX, 75390-9111, USA**USA
AUTHOR E-MAIL ADDRESS: Gang.Yu@UTSouthwestern.edu
JOURNAL: Journal of Biological Chemistry 277 (47): p45013-45019 November 22, 2002 2002
MEDIUM: print
ISSN: 0021-9258
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: %%%Presenilin%%% and %%%nicastrin%%% are essential components of the gamma-secretase complex that is required for the intramembrane proteolysis of an increasing number of membrane proteins including the amyloid-beta precursor protein (APP) and Notch. By using co-immunoprecipitation and nickel affinity pull-down approaches, we now show that mammalian APH-1 (mAPH-1), a conserved multipass membrane protein, physically associates with %%%nicastrin%%% and the heterodimers of the %%%presenilin%%% amino- and carboxyl-terminal fragments in %%%human%%% cell lines and in rat brain. Similar to the loss of %%%presenilin%%% or %%%nicastrin%%%, the inactivation of endogenous mAPH-1 using small interfering RNAs results in the decrease of %%%presenilin%%% levels, accumulation of gamma-secretase substrates (APP

carboxyl-terminal fragments), and reduction of gamma-secretase products (amyloid-beta peptides and the intra-cellular domains of APP and Notch). These data indicate that mAPH-1 is probably a functional component of the gamma-secretase complex required for the intramembrane proteolysis of APP and Notch.

? t s8/7/1-6

8/7/1
DIALOG(R)File 5:Biosis Previews(R)

18072665 BIOSIS NO.: 200400440584
New enzymes from environmental cassette arrays: Functional attributes of a phosphotransferase and an RNA-methyltransferase
AUTHOR: Nield Blair S; Willows Robert D; Torda Andrew E; Gillings Michael R ; Holmes Andrew J; Nevalainen K M Helena; Stokes H W; Mabbutt Bridget C (Reprint)
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JOURNAL: Protein Science 13 (6): p1651-1659 June 2004 2004
MEDIUM: print
ISSN: 0961-8368
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: By targeting gene cassettes by polymerase chain reaction (PCR) directly from environmentally derived DNA, we are able to amplify entire open reading frames (ORFs) independently of prior sequence knowledge. Approximately 10% of the mobile genes recovered by these means can be attributed to known protein families. Here we describe the characterization of two ORFs which show moderate homology to known proteins: (1) an aminoglycoside phosphotransferase displaying 25% sequence identity with APH(7") from Streptomyces hygroscopicus, and (2) an RNA methyltransferase sharing 25%-28% identity with a group of recently defined bacterial RNA methyltransferases distinct from the SpoU enzyme family. Our novel genes were expressed as recombinant products and assayed for appropriate enzyme activity. The aminoglycoside phosphotransferase displayed ATPase activity, consistent with the presence of characteristic Mg2+-binding residues. Unlike related %%%APH%%%(%%%4%%%) or APH(7") enzymes, however, this activity was not enhanced by hygromycin B or kanamycin, suggesting the normal substrate to be a different aminoglycoside. The RNA methyltransferase contains sequence motifs of the RNA methyltransferase superfamily, and our recombinant version showed methyltransferase activity with RNA. Our data confirm that gene cassettes present in the environment encode folded enzymes with novel sequence variation and demonstrable catalytic activity. Our PCR approach (cassette PCR) may be used to identify a diverse range of ORFs from any environmental sample, as well as to directly access the gene pool found in mobile gene cassettes commonly associated with integrons. This gene pool can be accessed from both cultured and uncultured microbial samples as a source of new enzymes and proteins.

8/7/2
DIALOG(R)File 5:Biosis Previews(R)

15385601 BIOSIS NO.: 200000103914
A novel Drosophila alkaline phosphatase specific to the ellipsoid body of the adult brain and the lower Malpighian (renal) tubule
AUTHOR: Yang Ming Yao; Wang Zongsheng; MacPherson Matthew; Dow Julian A T; Kaiser Kim (Reprint)
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JOURNAL: Genetics 154 (1): p285-297 Jan., 2000 2000
MEDIUM: print
ISSN: 0016-6731
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: Two independent Drosophila melanogaster P(GAL4) enhancer-trap lines revealed identical GAL4-directed expression patterns in the ellipsoid body of the brain and in the Malpighian (renal) tubules in the abdomen. Both P-element insertions mapped to the same chromosomal site (100B2). The genomic locus, as characterized by plasmid rescue of flanking DNA, restriction mapping, and DNA sequencing, revealed the two P(GAL4) elements to be inserted in opposite orientations, only 46 bp apart. Three genes flanking the insertions have been identified. Calcineurin A1 (previously mapped to 21E-F), lies to one side, and two very closely linked genes lie to the other. The nearer encodes %%%Aph%%%-%%%4%%%, the first Drosophila alkaline phosphatase gene to be identified; the more distant gene (1(3)96601) is novel, with a head-elevated expression, and with distant similarity to transcription regulatory elements. Both in situ hybridization with %%%Aph%%%-%%%4%%% probes and direct histochemical determination of alkaline phosphatase activity precisely matches the enhancer-trap pattern reported by the original lines. Although the P-element insertions are not recessive lethals, they display tubule phenotypes in both heterozygotes and homozygotes. Rates of fluid secretion in tubules from c507 homozygotes are reduced, both basally, and after stimulation by CAP2b, cAMP, or Drosophila leucokinin. The P-element insertions also disrupt the expression of %%%Aph%%%-%%%4%%% , causing misexpression in the tubule main segment. This disruption extends to tubule pigmentation, with c507 homozygotes displaying white-like transparent main segments. These results suggest that %%%Aph%%%-%%%4%%%, while possessing a very narrow range of expression, nonetheless plays an important role in epithelial function.

8/7/3
DIALOG(R)File 5:Biosis Previews(R)

14851623 BIOSIS NO.: 199900111283
Aminoglycoside phosphotransferases: Proteins, structure, and mechanism
AUTHOR: Wright Gerard D; Thompson Paul R (Reprint)
AUTHOR ADDRESS: Dep. Biochem., McMaster Univ., 1200 Main St. West, Hamilton, Ontario L8N 3Z5, Canada**Canada
JOURNAL: Frontiers in Bioscience 4 (CITED JAN. 19, 1999): pD9-21 Jan. 1,

1999 1999
MEDIUM: online
DOCUMENT TYPE: Article; Literature Review
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: Aminoglycoside antibiotics constitute an important class of clinically useful drugs which are imperiled by the emergence of resistant organisms. Aminoglycoside resistance in the clinics is primarily due to the presence of modifying enzymes which N-acetylate, O-adenylate or O-phosphorylate the antibiotics. The latter family of enzymes are termed the aminoglycoside phosphotransferases or kinases and are the subject of this review. There are seven classes of aminoglycoside phosphotransferases (APH(3'), APH(2"), APH(3"), APH(6), APH(9), %%%APH%%% (%%%4%%%), APH(7")) and many isozymes in each class, and although there is very little overall general sequence homology among these enzymes, certain signature residues and sequences are common. The recent determination of the three-dimensional structure of the broad spectrum aminoglycoside kinase APH(3')-IIIa complexed with the product ADP, in addition to mechanistic and mutagenic studies on this and related enzymes, has added a great deal to our understanding of this class of antibiotic resistance enzyme. In particular, the revelation of structural and mechanistic similarities between APHs and Ser/Thr and Tyr kinases has set the stage for future inhibition studies which could prove important in reversing aminoglycoside resistance.

8/7/4
DIALOG(R)File 5:Biosis Previews(R)

14713659 BIOSIS NO.: 199800507906
HER-2/neu expression as a progression marker in pancreatic intraepithelial neoplasia
AUTHOR: Tomaszewska Romana; Okon Krzysztof; Nowak Krystyna; Stachura Jerzy (Reprint)
AUTHOR ADDRESS: Dep. Pathomorphol., CMUJ, Grzegorzecka 16, 31-531 Krakow, Poland**Poland
JOURNAL: Polish Journal of Pathology 49 (2): p83-92 1998 1998
MEDIUM: print
ISSN: 1233-9687
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: Pancreatic intraepithelial neoplasia is only partially defined. Any attempt to establish the diagnostic criteria of early pancreatic carcinoma has been unsuccessful so far. In the present study we investigate expression of HER-2/neu in hyperplastic pancreatic duct epithelium. Material included resected pancreatic tissue obtained from 13 patients with pancreatic carcinoma, 11 with chronic pancreatitis, and 11 patients operated on for other reasons (gastric cancer, carcinoma of papilla Vateri). Hyperplasia of pancreatic duct epithelium was scored as: 1. flat mucosal hyperplasia FH, 2. papillary hyperplasia PH, 3. atypical papillary hyperplasia %%%APH%%%, %%%4%%%. carcinoma in situ CIS. Immunohistochemical expression of HER-2/neu was studied with the biotin-streptavidin method. Results were scored as: 1+ barely perceptible

light membranous rimming, 2+ light to moderate rimming, 3+ moderate to strong rimming. Expression of HER-2/neu paralleled with the hyperplasia grading, in most cases being negative in normal duct epithelium, weak in flat hyperplasia, and moderate to strong in atypical papillary hyperplasia and carcinoma in situ. In conclusion, HER-2/neu expression could be used as an additional marker of hyperplasia, dysplasia and atypia of pancreatic ductal and ductular epithelium in the process of pancreatic epithelial neoplasia. This could be especially useful in the cytological diagnosis of pancreatic intraepithelial neoplasia.

8/7/5
DIALOG(R)File 5:Biosis Previews(R)

12427869 BIOSIS NO.: 199497449154
Genetic diversity and multilocus associations in Cunninghamia lanceolata (Lamb.) Hook from the People's Republic of China
AUTHOR: Yeh F C (Reprint); Shi J; Yang R; Hong J; Ye Z
AUTHOR ADDRESS: Dep. Forest Sci., Univ. Alberta, Edmonton, AB T6G 2H1, Canada**Canada
JOURNAL: Theoretical and Applied Genetics 88 (3-4): p465-471 1994 1994
ISSN: 0040-5752
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: Open-pollinated seeds were assayed for allozyme polymorphisms at 24 loci to assess genetic diversity and multilocous associations in 16 populations of Cunninghamia lanceolata (Lamb.) Hook in the People's Republic of China. On average, the percentage of polymorphic loci was 88.0, the number of alleles per locus was 3.0, and the expected heterozygosity was 0.394. The distribution of genetic diversity was not correlated with the geographic and climatic variables of the populations. However, allele frequencies correlated linearly with the mean annual temperature of the populations at Mdh-1, Mdh-2, Mnr-2, Pgi-1, and Skdh-1 and with the altitude of the populations at %%%Aph%%%-%%%4%%% and 6Pg-2. Of the total gene diversity 6% was attributed to among population differentiation; 94% resided within populations. Two-locus gametic disequilibria were found in 15 of the 16 populations, and higher-order gametic disquilibria were significant in most populations. The gametic disequilibria did not correlate with geographic and climatic variables. The results suggest that population subdivision, founder effect, occurrence across diverse environments, a mating system dominated by inbreeding, and historical events from 2000 years of cultivation are contributing factors in the generation and maintenance of the multilocus genetic structure in this conifer.

8/7/6
DIALOG(R)File 5:Biosis Previews(R)

11259503 BIOSIS NO.: 199293102394
THE EFFECT OF GLUTAMATE RECEPTOR BLOCKADE ON ANOXIC DEPOLARIZATION AND CORTICAL SPREADING DEPRESSION
AUTHOR: LAURITZEN M (Reprint); HANSEN A J

AUTHOR ADDRESS: DEP GENERAL PHYSIOL BIOPHYSICS, PANUM INST, UNIV COPHENHAGEN, BLEGDAMSVEJ 3C, 2100-DK COPENHAGEN, DENMARK**DENMARK
JOURNAL: Journal of Cerebral Blood Flow and Metabolism 12 (2): p223-229 1992
ISSN: 0271-678X
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: ENGLISH

ABSTRACT: We examined the effect of blockade of N-methyl-D-aspartate (NMDA) and non-NMDA subtype glutamate receptors on anoxic depolarization (AD) and cortical spreading depression (CSD). [K+]e and the direct current (DC) potential were measured with microelectrodes in the cerebral cortex of barbiturate-anesthetized rats. NMDA blockade was achieved by injection of (+)-5-methyl-10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5,10-imine maleate [MK-801; 3 and 10 mg/kg] or amino-7-phosphonoheptanoate (%%%APH%%%; %%%4%%%.5 and 10 mg/kg). Non-NMDA receptor blockade was achieved by injection of 2,3-dihydroxy-6-nitro-7-sulfamoylbenzo(F)quinoxaline (NBQX; 10 and 20 mg/kg). MK-801 and APH blocked CSD, while NBQX did not. In control rats, the latency from circulatory arrest to AD was 2.1 .+-. 0.1 min, while the amplitude of the DC shift was 21 .+-. 1 mV, and [K+]e increased to 50 .+-. 6 mM. All variables remained unchanged in animals treated with MK-801, APH, or NBQX. Finally, MK-801 (14 mg/kg) and NBQX (40 mg/kg) were given in combination to examine the effect of total glutamate receptor blockade on AD. This combination slightly accelerated the onset of AD, probably owing to circulatory failure. In conclusion, AD was unaffected by glutamate receptor blockade. In contrast, NMDA receptors play a crucial role for CSD.

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9/7/110
DIALOG(R)File 5:Biosis Previews(R)

17053026 BIOSIS NO.: 200300011745
Association analysis between Alzheimer's disease and the %%%Nicastrin%%% gene polymorphisms.
AUTHOR: Orlacchio Antonio (Reprint); Kawarai Toshitaka; Polidoro Mario; Stefani Alessandro; Orlacchio Aldo; St George-Hyslop Peter H; Bernardi Giorgio
AUTHOR ADDRESS: Laboratorio di Neurogenetica, I.R.C.C.S. Santa Lucia, Via Ardeatina 354, 00179, Rome, Italy**Italy
AUTHOR E-MAIL ADDRESS: a.orlacchio@hsantalucia.it
JOURNAL: Neuroscience Letters 333 (2): p115-118 November 22, 2002 2002
MEDIUM: print
ISSN: 0304-3940 _(ISSN print)
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: The biological study of the %%%Nicastrin%%% protein shows its crucial role in the pathogenesis of Alzheimer's disease (AD). We tested the hypothesis that the %%%Nicastrin%%% (NCSTN) gene might be genetically

associated with AD. The association analysis of two single nucleotide polymorphisms (SNPs) in the coding region (cSNPs) of NCSTN were performed in an Italian population. No evidence of association was obtained between the two SNPs investigated in sporadic and familial AD cases under the stratification of currently known genetic risk factors including the apolipoprotein E (APOE), the presenilins and the beta-amyloid precursor protein. The result suggests no apparent synergic interaction between the NCSTN and APOE epsilon4 in the risk to develop the late onset sporadic form of AD. But considering its biological effects, the result can not exclude the NCSTN as candidate for genetic factor in AD. Further genetic study of the NCSTN would be necessary to evaluate the potential genetic involvement in AD.

9/7/111
DIALOG(R)File 5:Biosis Previews(R)

16920892 BIOSIS NO.: 200200514403
aph-1 and pen-2 are required for Notch pathway signaling, gamma-secretase cleavage of betaAPP, and presenilin protein accumulation
AUTHOR: Francis Ross; McGrath Garth; Zhang Jianhuan; Ruddy David A; Sym Mary; Apfeld Javier; Nicoll Monique; Maxwell Mark; Hai Bing; Ellis Michael C; Parks Annette L; Xu Wei; Li Jinhe; Gurney Mark; Myers Richard L; Himes Carol S; Hiebsch Ronald; Ruble Cara; Nye Jeffrey S; Curtis Daniel (Reprint)
AUTHOR ADDRESS: Exelixis, Inc., South San Francisco, CA, 94083, USA**USA
JOURNAL: Developmental Cell 3 (1): p85-97 July, 2002 2002
MEDIUM: print
ISSN: 1534-5807
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: Presenilins are components of the gamma-secretase protein complex that mediates intramembranous cleavage of betaAPP and Notch proteins. A C. elegans genetic screen revealed two genes, aph-1 and pen-2, encoding multipass transmembrane proteins, that interact strongly with sel-12/presenilin and aph-2/%%%nicastrin%%%. %%%Human%%% aph-1 and pen-2 partially rescue the C. elegans mutant phenotypes, demonstrating conserved functions. The %%%human%%% genes must be provided together to rescue the mutant phenotypes, and the inclusion of presenilin-1 improves rescue, suggesting that they interact closely with each other and with presenilin. RNAi-mediated inactivation of aph-1, pen-2, or %%%nicastrin%%% in cultured Dropsophila cells reduces gamma-secretase cleavage of betaAPP and Notch substrates and reduces the levels of processed presenilin. aph-1 and pen-2, like %%%nicastrin%%%, are required for the activity and accumulation of gamma-secretase.

9/7/112
DIALOG(R)File 5:Biosis Previews(R)

16920884 BIOSIS NO.: 200200514395
Genetics leads the way to the accomplices of presenilins
AUTHOR: Goutte Caroline (Reprint)

AUTHOR ADDRESS: Department of Biology, Amherst College, Amherst, MA, 01002, USA**USA
JOURNAL: Developmental Cell 3 (1): p6-7 July, 2002 2002
MEDIUM: print
ISSN: 1534-5807
DOCUMENT TYPE: Article
RECORD TYPE: Citation
LANGUAGE: English

9/7/113
DIALOG(R)File 5:Biosis Previews(R)

16805179 BIOSIS NO.: 200200398690
Presenilin 1 is required for maturation and cell surface accumulation of %%%nicastrin%%%
AUTHOR: Leem Jae Yoon; Vijayan Shrijay; Han Ping; Cai Dongming; Machura Michael; Lopes Kryslaine O; Veselits Margaret L; Xu Huaxi; Thinakaran Gopal (Reprint)
AUTHOR ADDRESS: Dept. of Neurobiology, Pharmacology and Physiology, Center for Molecular Neurobiology, The University of Chicago, 924 East 57th St., Knapp R212, Chicago, IL, 60637, USA**USA
JOURNAL: Journal of Biological Chemistry 277 (21): p19236-19240 May 24, 2002 2002
MEDIUM: print
ISSN: 0021-9258
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: Proteolytic processing of amyloid precursor protein generates beta-amyloid (Abeta) peptides that are deposited in senile plaques in brains of aged individuals and patients with Alzheimer's disease. Presenilins (PS1 and PS2) facilitate the final step in Abeta production, the intramembranous gamma-secretase cleavage of amyloid precursor protein. Biochemical and pharmacological evidence support a catalytic or accessory role for PS1 in gamma-secretase cleavage, as well as a regulatory role in select membrane protein trafficking. In this report, we demonstrate that PS1 is required for maturation and cell surface accumulation of %%%nicastrin%%%, an integral component of the multimeric gamma-secretase complex. Using kinetic labeling studies we show that in PS1-/-/PS2-/- cells %%%nicastrin%%% fails to reach the medial Golgi compartment, and as a consequence, is incompletely glycosylated. Stable expression of %%%human%%% PS1 restores these deficiencies in PS1-/- fibroblasts. Moreover, membrane fractionation studies show co-localization of PS1 fragments with mature %%%nicastrin%%%. These results indicate a novel chaperone-type role for PS1 and PS2 in facilitating %%%nicastrin%%% maturation and transport in the early biosynthetic compartments. Our findings are consistent with PS1 influencing gamma-secretase processing at multiple steps, including maturation and intracellular trafficking of substrates and component(s) of the gamma-secretase complex.

9/7/114
DIALOG(R)File 5:Biosis Previews(R)

16763499 BIOSIS NO.: 200200357010
Structure and expression of Strabismus 1 gene on %%%human%%% chromosome 1q21-q23
AUTHOR: Katoh Masaru (Reprint)
AUTHOR ADDRESS: Genetics and Cell Biology Section, Genetics Division, National Cancer Center Research Institute, Tsukiji 5-chome, Chuo-ku, Tokyo, 104-0045, Japan**Japan
JOURNAL: International Journal of Oncology 20 (6): p1197-1203 June, 2002 2002
MEDIUM: print
ISSN: 1019-6439
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: Xenopus Strabismus (Stbm) is a negative regulator of the WNT - beta-catenin signaling pathway. Strabismus 1 (STB1/VANGL2) and Strabismus 2 (STB2/VANGL1) are %%%human%%% homologues of Xenopus Stbm and Drosophila Stbm/Van Gogh (Vang) STB1 and STB2 are four-transmembrane-type proteins with Dishevelled-binding motif. STB2 and CASQ2 genes are located on %%%human%%% chromosome 1p13.3-p11 with an interval less than 5 kb. Here, STB1 gene and CASQ1 gene were found to be located on %%%human%%% chromosome 1q21-q23 with an interval of about 210 kb including %%%Nicastrin%%%, COPA, PXF, H326 and PEA15 genes. Exon-intron structure was well conserved between STB1 and STB2 genes. STB1-CASQ1 gene cluster and STB2-CASQ2 gene cluster might be generated due to duplication of ancestral gene cluster, and several genes might be inserted into the STB1-CASQ1 intergenic region during or after gene-cluster duplication. STB1 mRNA was relatively highly expressed in prostate, trachea, thymus, lymph node, placenta, fetal kidney, fetal brain, and fetal lung. In adult brain, STB1 mRNA was more highly expressed in cerebellum, corpus callosum, amygdala, and medulla oblongata. STB1 mRNA was moderately expressed in K-562 (chronic myelogenous leukemia), G-361 (melanoma), and MKN7 (gastric cancer). On the other hand, STB1 mRNA was almost undetectable in several %%%human%%% cancer cell lines, and was down-regulated in 4 out of 14 cases of primary kidney tumors, and in 2 out of 3 cases of primary lung cancer. Loss-of-function mutation of STB1 gene might lead to carcinogenesis through activation of the WNT - beta-catenin signaling pathway.

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DIALOG(R)File 5:Biosis Previews(R)

16748622 BIOSIS NO.: 200200342133
The gene encoding %%%nicastrin%%%, a major gamma-secretase component, modifies risk for familial early-onset Alzheimer disease in a Dutch population-based sample
AUTHOR: Dermaut Bart; Theuns Jessie; Sleegers Kristel; Hasegawa Hiroshi; van den Broeck Marleen; Vennekens Krist'l; Corsmit Ellen; St George-Hyslop Peter; Cruts Marc; van Duijn Cornelia M; Van Broeckhoven Christine (Reprint)
AUTHOR ADDRESS: Department of Molecular Genetics, University of Antwerp (UIA), Universiteitsplein 1, VIB8, B-2610, Antwerpen, Belgium**Belgium

JOURNAL: American Journal of Human Genetics 70 (6): p1568-1574 June, 2002
2002
MEDIUM: print
ISSN: 0002-9297
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: %%%Nicastrin%%% regulates gamma-secretase cleavage of the amyloid precursor protein by forming complexes with presenilins, in which most mutations causing familial early-onset Alzheimer disease (EOAD) have been found. The gene encoding %%%nicastrin%%% (NCSTN) maps to 1q23, a region that has been linked and associated with late-onset Alzheimer disease (LOAD) in various genome screens. In 78 familial EOAD cases, we found 14 NCSTN single-nucleotide polymorphisms (SNPs): 10 intronic SNPs, 3 silent mutations, and 1 missense mutation (N417Y). N417Y is unlikely to be pathogenic, since it did not alter amyloid beta secretion in an in vitro assay and its frequency was similar in case and control subjects. However, SNP haplotype estimation in two population-based series of Dutch patients with EOAD (n=116) and LOAD (n=240) indicated that the frequency of one SNP haplotype (HapB) was higher in the group with familial EOAD (7%), compared with the LOAD group (3%) and control group (3%). In patients with familial EOAD without the APOE epsilon4 allele, the HapB frequency further increased, to 14%, resulting in a fourfold increased risk (odds ratio=4.1; 95% confidence interval 1.2-13.3; P=.01). These results are compatible with an important role of gamma-secretase dysfunction in the etiology of familial EOAD.

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DIALOG(R)File 5:Biosis Previews(R)

16701687 BIOSIS NO.: 200200295198
gamma-Secretase, Notch, Abeta and Alzheimer's disease: Where do the presenilins fit in?
AUTHOR: Sisodia Sangram S; St George-Hyslop Peter H (Reprint)
AUTHOR ADDRESS: Centre for Research in Neurodegenerative Diseases and Department of Medicine, Dept of Medicine (Neurology), University of Toronto, Toronto Western Hospital, Toronto, ON, M5S 3H2, Canada**Canada
JOURNAL: Nature Reviews Neuroscience 3 (4): p281-290 April, 2002 2002
MEDIUM: print
ISSN: 1471-003X
DOCUMENT TYPE: Article; Literature Review
RECORD TYPE: Citation
LANGUAGE: English

9/7/117
DIALOG(R)File 5:Biosis Previews(R)

16520539 BIOSIS NO.: 200200114050
Wild-type and mutated nicastrins do not display aminopeptidase M- and B-like activities
AUTHOR: Fergani Anissa; Yu G; St George-Hyslop Peter; Checler Frederic (Reprint)

AUTHOR ADDRESS: IPMC du CNRS, UMR6097, 660 route des Lucioles, 06560, Valbonne, France**France
JOURNAL: Biochemical and Biophysical Research Communications 289 (3): p 678-680 December 7, 2001 2001
MEDIUM: print
ISSN: 0006-291X
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: %%%Nicastrin%%% is a recently discovered protein interacting with presenilins and the beta-amyloid precursor protein, the proteins playing key roles in Alzheimer's disease and which, when mutated, appear responsible for early-onset familial forms of Alzheimer's disease. %%%Nicastrin%%% was reported to modulate beta-amyloid production, a phenotype affected differently by missense mutations or deletions of a conserved hydrophilic domain. In addition to such a function, %%%nicastrin%%% was recently suggested to possess putative catalytic activity based on its sequence homology with enzymes of the aminopeptidase family. We set up stably transfected %%%human%%% HEK293 cells expressing either wildtype or mutated nicastrins and we show that these proteins do not exhibit aminopeptidase M- and B-like activities.

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DIALOG(R)File 5:Biosis Previews(R)

16518003 BIOSIS NO.: 200200111514
APH-2/%%%nicastrin%%% functions in LIN-12/Notch signaling in the Caenorhabditis elegans somatic gonad
AUTHOR: Levitan Diane (Reprint); Yu Gang; Hyslop Peter St George; Goutte Caroline
AUTHOR ADDRESS: Schering-Plough Research Institute, 2015 Galloping Hill Road, Kenilworth, NJ, 07033, USA**USA
JOURNAL: Developmental Biology 240 (2): p654-661 December 15, 2001 2001
MEDIUM: print
ISSN: 0012-1606
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: %%%Nicastrin%%% is a recently identified member of high-molecular weight complexes containing presenilin. The Caenorhabditis elegans homolog of %%%nicastrin%%%, aph-2, was shown to be required for GLP-1/Notch signaling in the early embryo. In addition to the maternal-effect embryonic lethal phenotype, aph-2 mutant animals also display an egg-laying defect. We show that this latter defect is related to the SEL-12/presenilin egg-laying defect. We also show that aph-2 and sel-12 genetically interact and cooperate to regulate LIN-12/Notch signaling in the development of the somatic gonad. In addition, aph-2 and lin-12/Notch genetically interact. We illustrate a new role for aph-2 in facilitating lin-12 signaling in the somatic gonad, thus providing evidence that APH-2 is involved in both GLP-1/Notch- and LIN-12/Notch-mediated signaling events. Finally, we demonstrate that %%%nicastrin%%% can partially substitute for aph-2, suggesting a conservation of function between these proteins.

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DIALOG(R)File 5:Biosis Previews(R)

16375933 BIOSIS NO.: 200100547772
Acyl-coenzyme A: Cholesterol acyltransferase (ACAT) modulates the generation of the amyloid b-peptide
AUTHOR: Puglielli L (Reprint); MacKenzie Ingano L A (Reprint); Tanzi R E (Reprint); Kovacs D M (Reprint)
AUTHOR ADDRESS: Genetics and Aging Unit, Dept. of Neurology, Massachusetts General Hospital, Charlestown, MA, USA**USA
JOURNAL: Society for Neuroscience Abstracts 27 (2): p1518 2001 2001
MEDIUM: print
CONFERENCE/MEETING: 31st Annual Meeting of the Society for Neuroscience San Diego, California, USA November 10-15, 2001; 20011110
ISSN: 0190-5295
DOCUMENT TYPE: Meeting; Meeting Abstract
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: Recent epidemiological studies have suggested a direct relationship between serum cholesterol levels and Alzheimer's disease (AD). Moreover, in vitro and in vivo studies have identified a direct association of APP and Abeta with cholesterol-rich domains as well as a regulatory effect of cholesterol levels on APP processing and Abeta generation. Previously, we presented genetic evidence that intracellular cholesterol distribution between the pool of free and esters (CEs) rather than total cholesterol levels affect Abeta generation. Here we demonstrate that acyl-coenzyme A: cholesterol acyltransferase (ACAT), the enzyme that catalyzes the formation of CEs, modulates APP processing and Abeta generation. ACAT competitive inhibitors reduced both CE levels and Abeta production by apprx35-40% in CHO (Chinese Hamster Ovary) cells and primary neurons from Tg2576 (APP695/swe) transgenic mice. ACAT inhibition also decreased the steady-state levels of alpha- and beta-C-terminal fragments of APP (APP-CTF) in the above cells, and in H4 (%%%human%%% neuroglioma) and SY5Y (%%%human%%% neuroblastoma) cells. Y-secretase cleavage of APP also diminished, as shown in stably transfected H4 cells by reduced cleavage of APPC105, a short APP-CTF. In contrast, no effect was observed on the steady-state levels of BACE and %%%nicastrin%%%, the cleavage of full-length Notch by furin, and of tumor necrosis factor-alpha (TNF-alpha) by TACE. In conclusion, our results indicate that ACAT activity regulates Abeta generation and that ACAT inhibitors may represent a novel strategy for the therapeutic treatment of AD.

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DIALOG(R)File 5:Biosis Previews(R)

16375266 BIOSIS NO.: 200100547105
Cell type specific effects of %%%Nicastrin%%% on amyloid-beta precursor protein processing
AUTHOR: Murphy M P (Reprint); Das P (Reprint); Nyborg A C (Reprint); McLendon D C (Reprint); Loosbrock N M (Reprint); Jansen K R (Reprint); Rochette M J (Reprint); Piper S C (Reprint); Golde T E (Reprint)

AUTHOR ADDRESS: Department of Neuroscience, Mayo Clinic Jacksonville, Jacksonville, FL, USA**USA
JOURNAL: Society for Neuroscience Abstracts 27 (1): p1218 2001 2001
MEDIUM: print
CONFERENCE/MEETING: 31st Annual Meeting of the Society for Neuroscience San Diego, California, USA November 10-15, 2001; 20011110
ISSN: 0190-5295
DOCUMENT TYPE: Meeting; Meeting Abstract
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: gamma-Secretase cleavage is the final proteolytic step that releases Abeta from the amyloid-beta protein precursor (APP). Biochemical and genetic evidence implicates presenilins (PS) as either catalytic components or essential co-factors in a high molecular weight gamma-secretase complex. Recently %%%Nicastrin%%%, a novel PS-associated, transmembrane glycoprotein, was identified as a putative functional unit of this complex (Yu et. al., Nature, 407:48, 2000). We have now extended these initial studies from %%%human%%% embryonic kidney 293 cells (HEK293) to additional cell types: HEK293T, CHO, H4, M17 and N2A, through both transient and stable expression systems. The effects on APP processing and Abeta production accompanying the expression of wild-type and mutant forms of %%%Nicastrin%%% (DELTA312-340, DELTA312-369, and D336A/Y337A) differed significantly between cell lines. In general, mutant %%%Nicastrin%%% caused a small but significant reduction in Abeta production from some cell lines but not others, and, in most cases, an accompanying 1.5-2x fold increase in secreted APP. Subcellular fractionation studies indicated that, in cell lines where mutant %%%Nicastrin%%% lowered Abeta production, less %%%Nicastrin%%% was found in lipid raft fractions that also contained gamma-secretase activity. In mouse brain, %%%Nicastrin%%% exclusively co-localized with the buoyant lipid raft fractions that contained PS, APP C-terminal fragments and gamma-secretase activity. These results provide additional evidence that %%%Nicastrin%%% is part of the active gamma-secretase complex, but also suggest that elucidating its actual role may entail careful consideration of the model system used.

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DIALOG(R)File 5:Biosis Previews(R)

16368820 BIOSIS NO.: 200100540659
Binding of %%%nicastrin%%% with presenilin-1 and effects on gamma secretase processing
AUTHOR: Kim S (Reprint); Yu C (Reprint); Chu S (Reprint); Xu H; Sisodia S S (Reprint)
AUTHOR ADDRESS: Dept Neurobiol Pharmacol Physiol, Univ Chicago, Chicago, IL, USA**USA
JOURNAL: Society for Neuroscience Abstracts 27 (1): p1219 2001 2001
MEDIUM: print
CONFERENCE/MEETING: 31st Annual Meeting of the Society for Neuroscience San Diego, California, USA November 10-15, 2001; 20011110
ISSN: 0190-5295
DOCUMENT TYPE: Meeting; Meeting Abstract
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: Intramembraneous cleavage of APP and Notch by gamma-secretase is mediated by a macromolecular complex that contains presenilins (PS1 and PS2), polytopic membrane proteins mutated in early-onset familial Alzheimer's disease. A novel type I membrane protein termed %%%nicastrin%%% has been immunoisolated using PS1 antibodies, that appears to modulate the production of Abeta peptides (Yu et al., Nature 407; 48-54, 2000). We show that, in mouse brain extracts, less than 10% of %%%nicastrin%%% is present in the PS1 complex (apprx700 kD). In stable %%%human%%% embryonic kidney 293 and mouse neuroblastoma N2a cell lines, %%%nicastrin%%% is expressed as a apprx100 kD glycoprotein, that is preponderantly localized in the ER and coresident with PS1. In stable cells expressing wild type %%%nicastrin%%%, significant amounts of endogenous PS1 fragments are coimmunoprecipitated with %%%nicastrin%%%; %%%nicastrin%%% appears to be stoichiometrically associated with the PS1-NTF and CTF complex. However, very low levels of full length APP, but not APP-CTFs, are coimmunoprecipitated with %%%nicastrin%%%. Deletion of residues 312-369 in the %%%nicastrin%%% ectodomain almost completely abrogates the binding with PS1. However, we do not detect any differences in the levels of APP-CTFs or secreted Abeta peptides between wild type and deletion mutant %%%nicastrin%%% expressing cells, as has been reported. These results suggest that %%%nicastrin%%% is a component of the PS1 complex, but association with PS1 is not a requirement for gamma-secretase activity. Ongoing studies are focused on the isolation of another components of the PS1 complex and their roles in gamma-secretase processing.

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Screening for %%%nicastrin%%% gene mutation and polymorphisms in Alzheimer's disease patients
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JOURNAL: Society for Neuroscience Abstracts 27 (1): p508 2001 2001
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ABSTRACT: %%%Nicastrin%%%, a newly cloned transmembrane glycoprotein, is reported to play critical roles with presenilins for amyloid beta protein processing and Notch signaling. We performed extended %%%nicastrin%%% gene screening to identify the pathogenic mutation(s) and the polymorphism(s) for Alzheimer's disease (AD) in Japanese population. Genomic PCR followed by single strand conformational polymorphisms (SSCP) analysis with silver staining was employed for screening. The PCR products showing differentially migrated band(s) in SSCP analysis were

subjected to direct sequence analysis. The genomic DNA samples from 10 patients with familial Alzheimer's disease (FAD) (3 of early-onset FAD and 7 of late-onset FAD), 34 patients with early-onset AD and 48 patients with late-onset AD were tested. No pathogenic mutations in FAD patients were found. We found 3 silent polymorphisms (L212L, D249D and S361S) and an intronic polymorphism. These polymorphisms were in complete disequilibrium, predicted to form a haplotype of %%%nicastrin%%% gene. The distributions of these polymorphisms (haplotype) were 9.2% in AD samples (n=198) and 7.9% in age-matched control subjects without statistical difference. These data indicate that the pathogenic mutation of %%%nicastrin%%% gene is rare in FAD and the identified %%%nicastrin%%% gene polymorphisms (haplotype) might not be genetic risk factor for sporadic AD.

16269566 BIOSIS NO.: 200100441405
%%%Nicastrin%%% binds to membrane-tethered Notch
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JOURNAL: Nature Cell Biology 3 (8): p751-754 August, 2001 2001
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ABSTRACT: The presenilins and %%%nicastrin%%%, a type 1 transmembrane glycoprotein, form high molecular weight complexes that are involved in cleaving the beta-amyloid precursor protein (betaAPP) and Notch in their transmembrane domains. The former process (termed gamma-secretase cleavage) generates amyloid beta-peptide (Abeta), which is involved in the pathogenesis of Alzheimer's disease. The latter process (termed S3-site cleavage) generates Notch intracellular domain (NICD), which is involved in intercellular signalling. %%%Nicastrin%%% binds both full-length betaAPP and the substrates of gamma-secretase (C99- and C83-betaAPP fragments), and modulates the activity of gamma-secretase. Although absence of the Caenorhabditis elegans %%%nicastrin%%% homologue (aph-2) is known to cause an embryonic-lethal glp-1 phenotype, the role of %%%nicastrin%%% in this process has not been explored. Here we report that %%%nicastrin%%% binds to membrane-tethered forms of Notch (substrates for S3-site cleavage of Notch), and that, although mutations in the conserved 312-369 domain of %%%nicastrin%%% strongly modulate gamma-secretase, they only weakly modulate the S3-site cleavage of Notch. Thus, %%%nicastrin%%% has a similar role in processing Notch and betaAPP, but the 312-369 domain may have differential effects on these activities. In addition, we report that the Notch and betaAPP pathways do not

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  significantly compete with each other.
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